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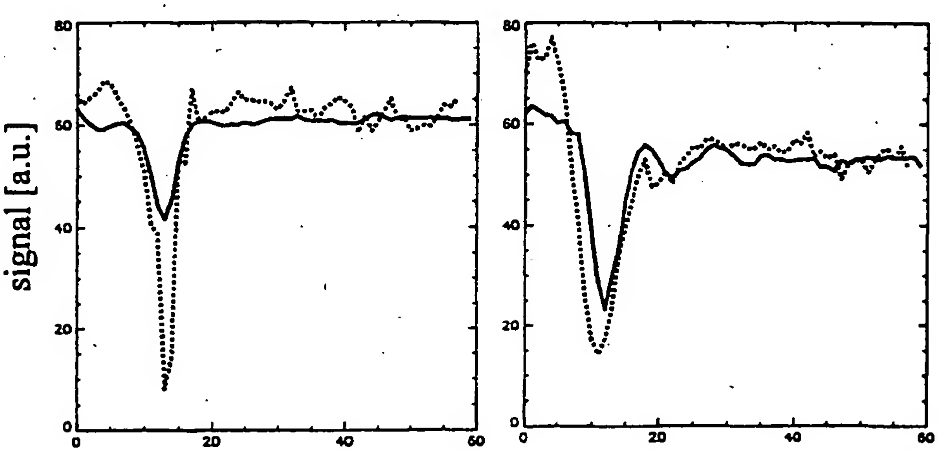
(54) Title: METHOD OF MAGNETIC RESONANCE IMAGING



(57) Abstract: A method of magnetic resonance imaging of the kidney in a vascularised human or non human body wherein a blood pool MR contrast agent, preferably a paramagnetic contrast agent, is administered as a bolus into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images. Preferably, T_2*-weighted images are generated during the first pass T_1. weighted images are generated after the concentration of contrast agent throughout the blood has become substantially uniform.

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Method of Magnetic Resonance Imaging

The present invention relates to improvements in and relating to methods of magnetic resonance imaging (MRI) of the kidneys.

Renal artery stenosis, the narrowing of the artery supplying blood to the kidney, can cause two effects - hypertension and renal insufficiency. Hypertension can result in large vessel disease and complications such as myocardial infarction and central nervous system bleeding. Renal insufficiency potentially leads to end stage renal failure resulting in the necessity for life-long dialysis and the risk of death. While renal artery stenosis is a relatively rare cause of hypertension affecting only 0.5 to 5% of the general population (see: Lewin et al., Arch. Intern. Med. 145: 424-427 (1985); Ying et al., N. Engl. J. Med. 311: 1070-1075 (1984); Swales, Lancet I: 577-579 (1976); and Arch. Intern. Med. 147: 820-829 (1987)), it has a high incidence in patients with pre-existing vascular disease. Moreover, in patients with diabetes the incidence rises to 10%, in patients with abdominal aortic aneurysms the incidence rises to over 20%, and in patients with peripheral vascular disease the incidence rises to over 40% (see: Sawicki et al., J. Intern. Med. 229: 489-492 (1991); and Missouris et al., Am. J. Med. 96: 10-14 (1994)).

Assessment of renal artery stenosis however is problematic for several reasons. Firstly, reliable detection and gradation of severity of the stenosis is required and in order to screen a large population of patients the procedure used must be safe, cost effective and accurate. Secondly, if the presence of a renal artery stenosis is detected, it is important to determine whether this is actually related to the patient's hypertension or renal insufficiency since only 10% of renal disease is due to renovascular

abnormalities with the rest generally being caused by diseases of the renal parenchyma, e.g. inflammatory diseases such as glomerulonephritis. Nonetheless chronic ischemia arising from renal artery stenosis can cause pathological changes to the renal parenchyma. Thirdly, since renoparenchymal and renovascular diseases can co-exist, it is important to determine the extent to which a renal artery stenosis is contributing to the overall malfunctioning of the kidney, i.e. to determine the hemodynamic and functional significance of the stenosis. Fourthly and most importantly, it is important to determine whether the benefit to the patient's renal function from removal of a renal artery stenosis will outweigh the risks of intervention. Moreover, there is only limited capacity for surgical revascularisation of patients with renal artery stenosis and the enormous costs of dialysis and organ transplant could be significantly reduced if the most appropriate candidates for surgical revascularisation can be selected.

Until now, the "gold standard" for diagnosis of renal artery stenosis has been X-ray digital subtraction angiography (DSA). However this technique is invasive since it involves catheterisation of the aorta and exposure of the patient to ionizing radiation and to renally excreted (and hence potentially nephrotoxic) contrast media. The problem of nephrotoxicity is particularly worrying since most patients investigated already suffer from some degree of renal insufficiency. Due to these drawbacks DSA is not considered particularly useful as a general screening technique. Furthermore, DSA is not able to quantify the extent of parenchymal damage and so is limited in its ability to be used in predicting the overall outcome of renal revascularisation. Other techniques for diagnosis of renal artery stenosis exist which involve ultrasound or renal scintigraphy and are non-invasive. However while

such techniques allow an assessment of renal function they do not permit accurate assessment of vascular morphology. Nonetheless, scintigraphy is currently considered to be the gold standard for measurement of renal perfusion and excretory function.

MRI has the great attractions of being non-invasive and allowing combination of multiple imaging strategies permitting both functional and morphological evaluation of the organ or tissue under investigation. While initially the emphasis in MRI was on imaging areas of the body without motion (e.g. the brain) and abdominal MRI, e.g. renal MR angiography, was subject to artefacts and not widely used, within recent years faster imaging procedures allowing image acquisition in less than a second have been developed and the area of MRI application has expanded into the chest and abdomen.

The introduction of contrast enhanced 3D MR angiography in a single breath-hold has allowed high quality angiography to be performed without the serious potential for nephrotoxicity (see: Prince et al., Radiology 197: 785-792 (1995)). The sensitivity and specificity of the technique for detection of a renal artery stenosis are now consistently reported as being about 95% (see: Hany et al., Radiology 204: 357-362 (1997); Snidow et al., Radiology 198: 725-732 (1996); Steffens et al., JMRI 7: 617-622 (1997); Bakker et al., Radiology 207: 497-504 (1998); and Wilman et al., Radiology 205: 137-146 (1997)).

This MRI technique however still suffers from various drawbacks. Firstly it is still relatively complex since, using the injectable MRI contrast agents currently commercially available (e.g. Magnevist, Omniscan or ProHance), image acquisition must be timed to coincide with the first passage of the agent through the renal arteries (for example using the technique of EP-B-656762 (Prince)) as these agents rapidly extravasate. Although a variety of techniques for

automatic or semi-automatic detection of contrast agent arrival have been developed (see for example Schoenberg et al., Invest Radiol. 33: 506-514 (1998)), image acquisition timing is still a complex issue.

Secondly, the spatial resolution achievable with first pass 3D MR angiography is three to five-fold lower than that of DSA. First pass imaging requires maximum coverage of the vessels of interest in a single breath-hold and thus wastes spatial resolution.

Thirdly, MR imaging using extracellular (ECF) contrast agents, such as the soluble gadolinium monochelates that are currently commercially available, cannot absolutely quantify the amount of parenchymal damage to the kidney since the kidney does not have a blood tissue barrier and the ECF agents immediately extravasate when passing through the glomeruli. Accordingly quantification of blood volume and blood flow is not feasible.

There is thus a need for an improved method of MRI which can be used to assess both renal function and morphology.

We have now found that quantification of both the morphological degree of renal artery stenosis and the renal parenchymal perfusion can be achieved in a single MR examination if a blood pool contrast agent, i.e. a contrast agent which remains in the intravascular space during the time course of the examination is used.

Viewed from one aspect the present invention thus provides a method of magnetic resonance imaging of the kidney in a vascularised human or non human (e.g. mammalian, avian or reptilian) body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and

renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms.

By a blood pool MR contrast agent is meant a magnetic (e.g. paramagnetic, ferromagnetic, ferrimagnetic or superparamagnetic) material capable of reducing the T_1 and/or T_2* of water protons and which if administered into the vascular space does not significantly leak out into the interstitium during the time course of the interventional or interoperative procedure, i.e. it is essentially confined to the vascular space until excreted or metabolized. Examples of such blood pool agents include polymeric chelates (e.g. cascade polymers or dendrimers carrying metallated chelate groups) and particulates, in particular iron oxides and liposomes. Generally the agent should have a blood half life of at least 5 minutes, preferably at least 30 minutes. By way of contrast, the first parenteral MR contrast agents Gd DTPA (Magnevist® from Schering), Gd DTPA-bismethylamide (Omniscan® from Nycomed Amersham) and Gd HP-D03A (ProHance®) are all extracellular fluid MR agents; they are water-soluble mono-chelates which following administration into the vasculature rapidly extravasate into the interstitium.

Blood pool agents of particular use in the method of this invention include low molecular weight chelates which bind to blood proteins, e.g. blood proteins such as albumin, for example DTPA or DOTA derivatised with protein binding groups, e.g. lipophilic side chains such as aromatic moieties, e.g. one or more phenyl ring systems. One such example is MS-325/Angiomark of EPIX.

Suitable polymer based contrast agents for use in the method of the present invention can be carbohydrate or protein based, e.g. CMD-DTPA-Gd of Guerbet (Carboxymethyl dextran-GdDTPA conjugates), GdDTPA polylysine conjugates, or cascade or dendrimer polymers, e.g. Gadomer 17 of Schering AG or similar cascade

polymers as described in US-A-5874061 (of Schering AG), herein incorporated by reference.

Suitable iron oxide (or doped iron oxide) based contrast agents for use in the method of the present invention are known in the field under the name of SPIO (superparamagnetic iron oxides) or USPIO (ultrasmall superparamagnetic iron oxides). Examples include carbohydrate stabilised iron oxide particles, e.g. dextran-stabilised particles such as Combidex of Advanced Magnetics, and NC100150 (Clariscan, Nycomed Amersham).

More particularly the magnetic iron oxide contrast agent is preferably a water-dispersible material comprising magnetic iron oxide particles having on their surfaces (e.g. as a coating), an optionally modified carbohydrate or polysaccharide or derivative thereof, e.g. a glucose unit containing optionally modified polysaccharide or derivative thereof, preferably an optionally modified dextran or starch or derivative thereof, for example a cleaved (e.g. oxidatively cleaved) starch or carboxylated dextran. Such iron oxide complexes preferably also comprise a further material (e.g. coating material), especially one which inhibits opsonization, e.g. a hydrophilic polymer, preferably a functionalized polyalkylene oxide, more preferably a functionalized polyethylene glycol (PEG), in particular methoxy PEG phosphate (MPP).

The iron oxide complexes preferably have a core (i.e. iron oxide particle) diameter (mode diameter) of 1 to 15 nm, more preferably 2-10 nm, especially 3-7 nm, a total diameter (mode particle size) of 1 to 100 nm, more preferably 5-50 nm, especially preferably 10-25 nm, an r_2/r_1 ratio at 0.47T and 40°C of less than 3, more preferably less than 2.3, still more preferably less than 2.0, especially preferably less than 1.8. The saturation magnetization (Msat) at 1T is preferably 10 to 100 emu/gFe, more preferably 30-90 emu/gFe.

Other particulate based systems of use in the method of the present invention include liposomal or emulsion based agents.

Furthermore, compound 7228 of Advanced Magnetics can be used in the method of the present invention, as can the materials described in WO 91/12025, WO 90/01899, WO 88/00060, WO 91/12526 and WO 95/05669, all to Advanced Magnetics, and those described in WO92/11037 and WO90/01295, all of which publications are incorporated herein by reference.

Viewed from a further aspect the present invention provides the use of a blood pool MR contrast agent for the manufacture of a contrast medium for use in a method of diagnosis comprising a method of imaging according to the invention.

The comprehensive morphological and functional approach to kidney imaging according to the invention can be used to guide the therapeutic strategies for patients with renal artery stenosis by establishing guidelines for revascularisation since the quantitative data generated by the method of the invention can be correlated with each other to differentiate between renovascular and renoparenchymal damage.

The blood pool contrast agent is desirably administered as a bolus, e.g. by injection or infusion into the vasculature over a short time period, preferably 1 minute or less, more preferably 5 seconds or less, most preferably 1 second or less. The bolus may be sharpened by using a saline injection chaser. Injection or infusion is preferably into a vein upstream of the kidney. Particularly preferably injection is at a site whereby bolus arrival at the kidney will occur within 60 seconds, preferably 10 to 25 seconds. If a particularly sharp bolus is desired, injection may be into the renal artery itself.

In order to quantitate tissue perfusion (in terms of organ perfusion) in units of ml blood/min/g tissue)

the transient effect of the contrast agent in the tissue must be observed. This is best achieved by measuring the first pass effect of the agent in the tissue after a bolus injection of the agent.

The dosage of the contrast agent used according to the invention will depend upon the species, the longitudinal relaxivity of the agent, the magnetic moment of the agent at the imaging field strength and the sequence parameters used to acquire the image.

Concentration of a blood pool contrast agent is typically 0.01 - 10 mM in blood during examination.

The blood pool contrast agent is especially preferably a superparamagnetic iron oxide, e.g. as disclosed in WO97/25073, especially one coated with a starch residue and particularly one also coated with an opsonisation inhibitor such as for example PEG. The use of such contrast agents has been described by Røhl et al. Acta Radiologica <u>40</u>: 282-290 (1999). These materials are especially suitable since they combine a strong T_2* in a bolus phase with a predominant T_1 effect in the steady state. Furthermore, they remain in the vascular space during kidney transit, and they are not nephrotoxic and do not rely on renal excretion and so are particularly safe for use with patients with compromised renal function.

The MR imaging in the method of the invention preferably involves image acquisition at least two times, once during first passage of a bolus of the contrast agent through the kidney and a second after the contrast agent has become substantially uniformly distributed in the blood, e.g. after 1 to 30 minutes, preferably 3 to 15 minutes, following bolus administration of the contrast agent. Desirably the first image is T_1, T_2, or T_2*-weighted and the second T_1-weighted. Especially preferably, image generation is also affected before contrast agent administration or before arrival of the contrast agent at the kidney, i.e.

a native or non-contrast enhanced image is preferably acquired.

Thus, in a preferred embodiment, the invention provides a method of MR imaging of the kidney in a vascularised human or non-human animal body, said method comprising administering into the vasculature of said body a bolus of a blood pool MR contrast agent (e.g. intravenous injection), preferably a superparamagnetic contrast agent, generating a contrast-enhanced MR image, preferably a T_2*-weighted image, of said kidney during the first pass of said contrast agent, and after the concentration of said contrast agent throughout the blood of said body has become substantially uniform generating at least one further MR image, preferably a T_1-weighted image, of said kidney, and optionally deriving from said MR images values indicative of renal perfusion and renal artery stenosis grade.

In the methods of the invention, the first pass T_2*-weighted image, which essentially provides perfusion information, can be superimposed upon the subsequent T_1-weighted image, which provides morphological information so as to permit the physician to view directly the correlation between a stenosis and a hypoperfused or non-perfused area within the kidney.

As mentioned earlier, renal hypertension or insufficiency may be caused by renal artery stenosis or by parenchymal damage. Evaluation and grading of renal artery stenosis is achievable using the methods of the present invention, in particular where the steady state images are generated from a volumetric (3D) image acquisition, enabling reconstruction in any plane and any projection within the acquired volume. Assessment of parenchymal damage can be performed according to the methods of the invention by using the first pass images to quantify intra-parenchymal blood volume. The quantitative data thus generated from the two sets of images may then be correlated with each other to enable

the physician to differentiate between renovascular and renoparenchymal damage and assess the likelihood of success for interventional surgery.

Viewed from a further aspect, the invention thus provides a method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body, preferably as a bolus, and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein the physiological and morphological state of said kidney is assessed.

While many varieties of blood pool MR contrast agents may be used, e.g. macromolecular or polymeric (e.g. dendrimeric) agents, blood protein binding agents, liposomal contrast agents and superparamagnetic iron oxides, it is particularly desirable to use the degraded starch-coated superparamagnetic iron oxides of WO97/25073. These are especially suitable for four reasons. Firstly due to the large magnetization associated with superparamagnetic particles they have predominant T_2^* effects during the first pass of the bolus. Secondly, due to their low r_2/r_1 ratio, T_1 effects dominate when a steady state, i.e. when a uniform distribution within the blood pool, has been achieved. Thirdly, due to the size and surface of the particles they remain in the intravascular space during the time course of the MR examination being subject neither to glomalular filtration nor to secretion (their ultimate elimination from the intravascular space is via the reticuloendothelial system). Fourthly, they are not nephrotoxic and not renally excreted and thus are suitable for use with patients with compromised renal function.

Contrast enhanced MR angiography is preferably

effected using fast spoiled gradient echo sequences with short T_R and T_E values. A complete 3D data set with high spatial resolution can be obtained in this way because of the prolonged T_1 shortening effect and long vascular half life of the agent. To obtain MR angiograms sufficiently clear for diagnostic use, the T_1 of the blood needs to be reduced significantly - shorter T_1 of the blood, shorter T_R and higher flip angle result in higher contrast between the blood vessel and the surrounding tissues which will have higher T_1 values.

Desirably the blood pool MR contrast agent is administered at dosages sufficient to achieve T_1 values in blood, at steady state, of less than 300 ms, more preferably less than 200 ms and still more preferably less than 100 ms. T_1-weighted 3D spoiled gradient echo imaging is then preferably performed with T_R values of 1.5 to 50 ms, more preferably 2 to 20 ms, T_E values of 0.5 to 15 ms, more preferably 0.7 to 5 ms, and flip angles of 5 to 90, more preferably 10 to 60. Optionally a magnetisation preparation prepulse may be applied in order to increase the contrast between blood and surrounding tissues. The inversion time T1 should preferably be between 5 and 700 ms, more preferably between 10 and 600 ms, even more preferably between 15 and 500 ms. Although image acquisition following the prepulse is preferably a gradient echo sequence, echo planar (EPI) or RARE type acquisition schemes may also be applied. Since the blood pool MR contrast agent remains in the vasculature for a prolonged period, multiple breathold MR angiograms can be obtained. Generally one will first obtain a large volume data set with low spatial resolution and subsequently (having identified the region of interest) obtain small volume data sets with a higher spatial resolution, e.g. about 1 mm^3. These may be used to grade renal artery stenosis, e.g. in steps of 20%. A grade of 0% means blood flow is unaffected, while a grade of 100% means blood flow is

totally blocked. 50% can mean 50% reduction in arterial cross sectional area or 50% reduction in blood flow rate (i.e. mL/sec); for present purposes diameter is preferred. One clinically relevant grading scheme grades stenoses as 0%, less than 50%, 50 to 80%, and above 80% (see for example Hany et al. Radiology 204: 357-362 (1997), Snidow et al. Radiology 198: 725-732 (1996), Steffens et al. JMRI 7: 617-622 (1997), Bakker et al. Radiology 207: 497-504 (1998) and Wilman et al. Radiology 205: 137-146 (1997)).

In the method of the invention grading may be effected by measuring the vessel diameter at the point of maximum narrowing and the diameter of the normal vessel distal to the stenosis. The % stenosis is then determined from these two numbers.

The images which are used to grade renal artery stenosis may be digitally post-processed to remove overlaying renal veins if these otherwise affect interpretation of the stenosis. This may be achieved by selecting a projection in the 3D data set where the artery is not obscured by the vein. A vessel tracking algorithm may also be employed to identify the arterial structures.

Quantification of renal perfusion relies on the blood pool MR contrast agent being confined to the intravascular space during the course of the MR examination. In the methods of the invention the T_2^* properties of the contrast agent may be utilised in first pass imaging following bolus administration. However the T_1 properties of the contrast agent in the steady state may additionally or alternatively be used. In the T_2^* model, the MR signal variation in the tissue during the first pass of the contrast agent can be analysed according to any established tracer kinetic technique, e.g. using the methods of Schreiber et al. J. Cereb. Blood Flow Metab. 18: 1143 (1998) and Stritzke et al. IEEE Trans. Med. Imag. 9: 11 (1990).

For determination of blood flow per gram of tissue, the blood volume is divided by the mean transit time of the bolus, e.g. as described by Schreiber et al. in J. Cereb. Blood Flow Metals 18: 1143-1156 (1998). The mean transit time may be determined as shown in Schreiber et al. J. Cereb. Blood Flow Metab. 18: 1143 (1998), Remmp et al. Radiology 193: 637 (1994) and Stritzke et al. IEEE Trans. Med. Imag. 9: 11 (1990).

For the kidney, the renal artery (which supplies more than 99% of the blood to the kidney) may be used as the input function. A dual slice T_2^*-weighted sequence is desirably used for determination of the signal curve in the input function and the tissue. One slice is positioned perpendicular to the renal artery and the other is positioned perpendicular to the long axis of the kidney. In this way a sufficient amount of renal cortex and medulla is contained within the second slice. The contrast media bolus should be as tight as possible in order to minimise the contribution of T_1 effects to the signal curve. T_E is selected to be long enough to ensure T_2^* weighting but not so long that signal drops right down to base line. The temporal resolution should be selected to be high enough to avoid under-sampling of the signal curve. Image acquisition time is thus preferably 5 sec or less, more preferably 2 sec or less, particular 1 sec or less. With an image acquisition time of 2 sec, 5 to 7 data points can be obtained during bolus arrival in the renal artery. Sampling (i.e. image acquisition) should preferably continue until signal has returned to base line. Additionally, image acquisition should desirably be during free-breathing since breathold alters renal artery blood flow. Data points of images with substantial motion therefore may have to be corrected by post processing or removed from the signal curve. Using this approach absolute values of cortical perfusion can be obtained. The values obtained for non-stenosed kidneys of adult foxhounds ranged

between 4 and 5 mL/g/min which was in good agreement with invasively obtained and literature data.

Typically, such a T_2^*-weighted (i.e. T_2-weighted) imaging sequence may require flip angle values of 5 to 90°, more preferably 10 to 60°.

Alternatively or additionally, blood volume may be accomplished by T_1 mapping in the steady state. High resolution T_1-images of the kidney and aorta are obtained and the relative change in R_1 due to the agent in a large vessel is compared to the relative change in a given tissue. The fractional difference in R_1 in tissue versus vessel is then directly related to the blood volume of the tissue, e.g. using the method of Bauer et al. Magn. Reson. Med. 35: 43-55 (1996).

The methods of the invention may desirably also involve administration of pharmacological agents which affect blood flow, e.g. vasoconstructive or vasodilating agents or blood clot-dissolving agents, e.g. angioplasty (e.g. PCTA) or placement of a stent. In this way the physician can monitor the success of attempts to remove a stenosis.

A key issue in the comprehensive assessment and differentiation of renal disease is the systematic correlation of changes in renal perfusion to the morphological degree of renal artery stenosis. Thus in the Examples below, different states were simulated under controlled conditions.

In the dog model described in Example 1, different degrees of renal artery stenosis were artificially created with an invasively implanted rubber clamp. For each degree of stenosis, high-resolution MR angiograms as well as perfusion measurements were performed. The absolute values for cortical perfusion were correlated to the percentage of renal artery stenosis. For acutely induced renal artery stenoses in an otherwise healthy kidney, cortical perfusion remained constant over a large array of degrees of stenosis. Only stenoses

greater than 95% caused a substantial drop in parenchymal perfusion. These results demonstrate the uniqueness of the methods of the invention in two ways. First, this comprehensive approach obtains data that does not correlate linearly to the degree of stenosis and therefore does not provide redundant but rather additional information. Second, since there is a rather abrupt change of parenchymal perfusion, the cut-off point of exceeding the autoregulative capacity can be determined. Therefore, the functional significance of a stenosis can be quantified.

In addition, the methods of the invention were evaluated in chronic disease states. In patients with different degrees of renal artery stenosis, bilateral perfusion measurements were performed and the absolute values of cortical perfusion were correlated to the morphologic degree of renal artery stenosis obtained in the MR angiograms. By combined analysis of the morphologic and functional MR data, the following different disease states could be identified and differentiated based on the quantitative data:

- Low perfusion states with coexisting normal low-grade stenosis. This combination is caused by underlying primary renoparenchymal damage.
- Normal perfusion states with low-grade, functionally non-significant stenoses.
- Low perfusion states caused by the long presence of high-grade functionally significant stenoses.

The methods of the invention will now be illustrated further by the following non-limiting Examples and the accompanying drawings, in which:

Figure 1a shows contrast-enhanced MR angiograms obtained for different degrees of arterial stenosis (open arrow) in the same dog (left: no stenosis, middle: moderate (70%) stenosis, right high-grade (90%) stenosis);

Figure 1b shows T_2* weighted perfusion images

corresponding to each image in Fig 1a during peak arrival of the contrast agent bolus;

Figure 2a shows a contrast-enhanced MR angiogram revealing low-grade (~50%) stenosis (open arrow);

Figure 2b shows T_2* weighted perfusion images at peak arrival of the contrast agent bolus, revealing decreased perfusion in the left kidney (Fig 2b.1) and normal cortical perfusion in the right kidney (Fig 2b.2);

Figure 3 shows signal-time curves for the left (Fig 3a) and right (Fig 3b) kidney, corresponding to the images of Fig 2b.1 and 2b.2 respectively, showing input functions obtained in the left and right renal artery (dotted lines) and the resulting response curve in the corresponding cortical tissue (solid lines).

Example 1

Systematic correlation of the morphologic degree of stenosis to the corresponding perfusion changes in dogs

This Example demonstrates the systematic correlation between morphologic degree of stenosis and corresponding functional in terms of perfusion using both dynamic first pass and steady state imaging.

In a foxhound dog (weight approximately 30 kg) different degrees of renal artery stenosis were created by a rubber clamp, which was implanted around the renal artery. Angiographic and perfusion data were obtained using,

- bolus application of 1.5 ml of a 30 mg Fe/ml suspension of a superparamagnetic iron oxide prepared according to the description of Example 12 of WO97/25073, administered into the jugular vein at 5 mL/second,

- dynamic T_2^*-weighted perfusion imaging during first pass of the bolus for quantification of cortical blood flow (see Fig. 1b of the accompanying drawings),
- high-resolution contrast-enhanced MR angiography in the steady state (see Fig. 1a),
- estimation of the cortical blood volume in the steady state.

The images were recorded on a Siemens Vision 1.5T MR imaging apparatus using the following sequences:

The following results were obtained:

- In the high-resolution contrast-enhanced MR angiograms with a voxel size of 0.7 x 1.0 x 0.7mm, the different degrees of stenosis can be accurately identified as shown here for a non-stenosed artery (0%), a moderate stenosis (70%) and a high-grade stenosis (90%).
- The T_2^* weighted images obtained during first pass reveal specific findings for the different degrees of stenosis. In the non-stenosed (0%) vessel, a normal corticomedullar differentiation is found with massive signal loss in the cortex during peak arrival of the bolus. Only minor changes in the medulla are present as a result of overall much lower perfusion. Mean flow was calculated as 4.2 ± 1.1 ml per gram of cortical tissue per minute. For the moderate stenosis, no apparent changes in renal perfusion are visible. Cortical perfusion stays constant. This indicates that at least in the acute state the autoregulation of the kidney still is able to maintain adequate perfusion, therefore this stenosis reveals no functional significance. For the high-grade stenosis (90%), a substantial drop in cortical perfusion is found with loss of corticomedullar differentiation. Absolute cortical

perfusion drops down to 2.1 ± 0.6 ml/g/min. This indicates that the cut-off point of the autoregulative capacity has been exceeded for this degree of stenosis. The blood volume required for absolute quantification of the cortical blood flow can be also calculated in the steady state by means of T_1 measurements in the renal parenchyma and the aorta. This can be done for example using a saturation recovery gradient echo sequence (c) with varying inversion times, but this strategy is not limited to this particular technique.

A T_2*-weighted FLASH sequence was used with the following sequence parameters :T_R=15 ms, T_E=6 ms, flip angle=12 deg, FOV=200x200 mm, slice thickness=5 mm, scan time =1.92 secs. One slice was used to track the bolus passage of the agent in renal parenchyma, whereas the second slice was positioned perpendicular to the renal artery to measure the arterial input function (AIF). Signal-time-curves were converted to concentration-time curves according to an exponential relationship (see Schreiber et al. and Remmp et al. (both supra)). The tissue curves were deconvoluted with the AIF using a method based on the AIF by orthogonal functions (see Schreiber et al. and Stritzke et al. (both supra)).

According to the principles of indicator dilution theory, the region blood volume (rBV), regional blood flow (rBF) and mean transit time (MTT) were calculated in RIO's (150 to 280 pixel each) lying in the renal cortex and the medulla (see Schreiber et al., Remmp et al. and Stritzke et al. (all supra)).

The morphologic degree of stenosis, defined as the

percent change in artery diameter, was determined in the steady state. An additional 4.5 ml of the 30 mg Fe/ml suspension of the superparamagnetic iron oxide prepared according to the description of Example 12 of WO97/25073 was injected prior to imaging so that the total dose was 4.0 mg Fe/kg. Images were obtained using T_1-weighted 3D FEE sequences.

Example 2

Differentiation of renovascular and renoparenchymal disease in human patients

The comprehensive approach demonstrated in Example 1 was applied to a human subject and this differentiation of renoparenchymal damage from renovascular disease could be made based on the combined analysis of the angiographic and perfusion data. The patient presented with hypertension resistant to therapy and rising creatinine. The contrast-enhanced MR angiography performed in the steady state revealed only a low-grade stenosis of about 50% in the distal left renal artery (see Figure 2(a)), which was confirmed by conventional X-ray digital subtraction angiography. However, the dynamic T_2^* perfusion measurements demonstrated a dramatic decrease in cortical perfusion of the left kidney with loss of corticomedullar differentiation (see Figure 2(b.1)). Calculated mean cortical flow was only 1.8 ± 0.7 ml/g/ min (see Figure 3(a)). The normal right kidney revealed a cortical blood flow of about 4.2 ± 0.9 ml/g/min (see Figures 2(b.2) and 3(b)). The substantially smaller response of the left cortex can be seen by comparison of left (Fig 3a) and right (Fig 3b) response curves (solid lines). These findings were confirmed by Tc-99-MAG3-scintigraphy, which showed only 23% of the left kidney function remaining compared to

77% of the right kidney function. Based on these findings, the diagnosis of an underlying renoparenchymal damage could be established with coexistence of a non-functionally significant renal artery stenosis. Based on the comprehensive MR information the patient did not undergo surgery.

Claims

1. A method of magnetic resonance imaging of the kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and, optionally, values indicative of renal artery stenosis grade and renal perfusion are generated from said images or from detected magnetic resonance signals capable of transformation into said angiograms.

2. A method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a vascularised human or non human body wherein a blood pool MR contrast agent is administered into the vasculature of said body and images of said kidney are generated using imaging sequences and timing to permit both visualisation and gradation of renal artery stenosis and quantification of renal perfusion, and wherein the physiological and morphological state of said kidney is assessed.

3. A method as claimed in claim 1 or claim 2 wherein said blood pool MR contrast agent is a superparamagnetic contrast agent.

4. A method as claimed in any of claims 1 to 3 wherein said blood pool MR contrast agent comprises magnetic iron oxide particles having on their surfaces an optionally modified polysaccharide and optionally a material which inhibits opsonization.

5. A method as claimed in any of claims 1 to 4 wherein said blood pool MR contrast agent comprises

superparamagnetic iron oxide particles having on their surfaces degraded starch and optionally a functionalised PEG.

6. A method as claimed in any of claims 1 to 5 wherein said blood pool MR contrast agent is administered as a bolus.

7. A method of claim 6 wherein a contrast enhanced image of said kidney is generated during the first pass of said contrast agent.

8. A method of claim 7 wherein said image is a T_2*-weighted image.

9. A method of any of claims 6 to 8 wherein at least one further image of said kidney is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

10. A method of claim 9 wherein at least one T_1-weighted image is generated after the concentration of said contrast agent throughout the blood of said body has become substantially uniform.

11. A method of claim 9 or claim 10 comprising at least one further administration of said contrast agent.

12. A method of any of claims 1 to 11 wherein values indicative of renal perfusion and renal artery stenosis grade are derived from said MR images.

13. The use of a blood pool MR contrast agent for the manufacture of a contrast medium for use in a method of diagnosis comprising a method according to any of claims 1 to 12.

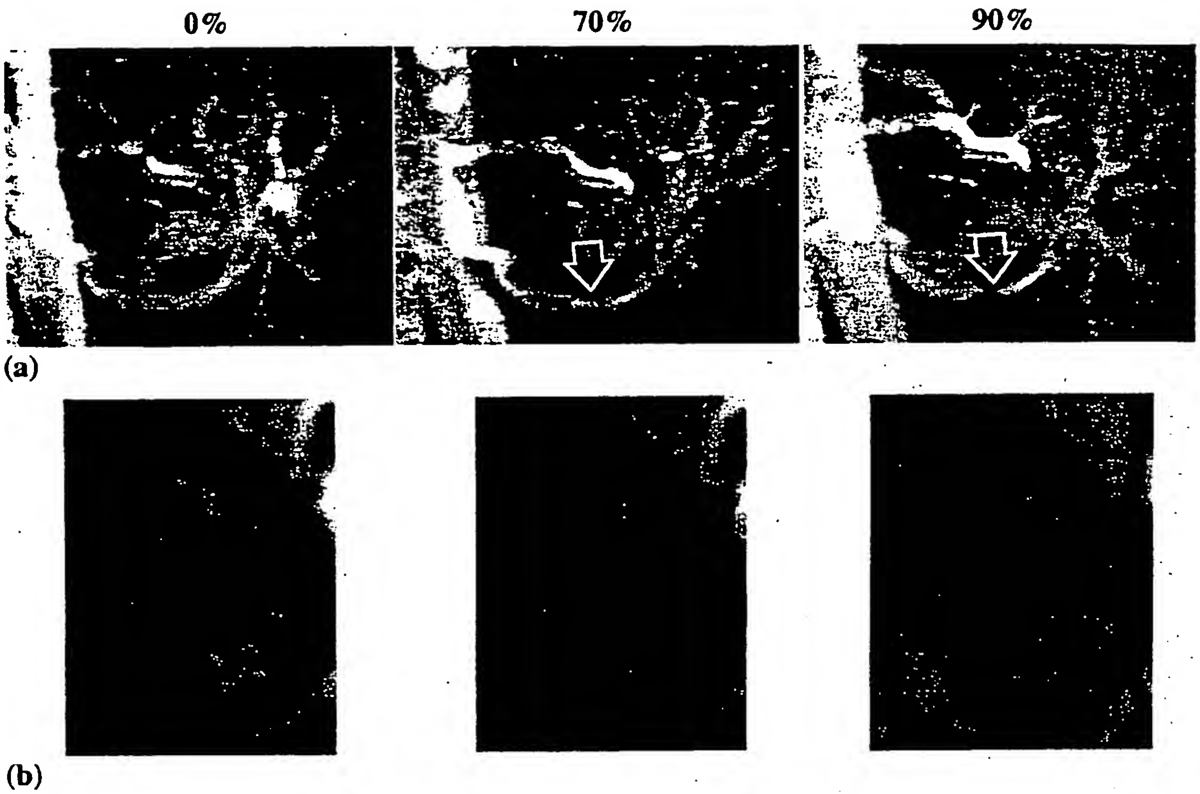


Fig 1

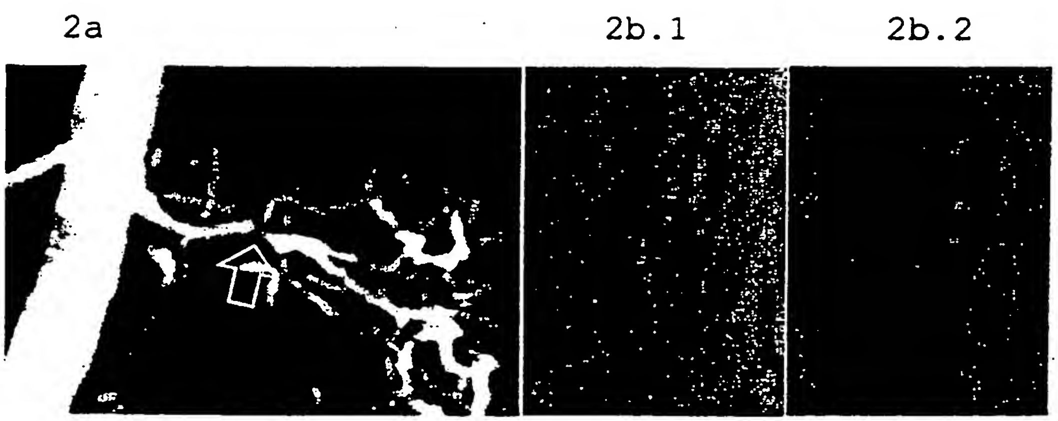


Fig 2

Fig 3a

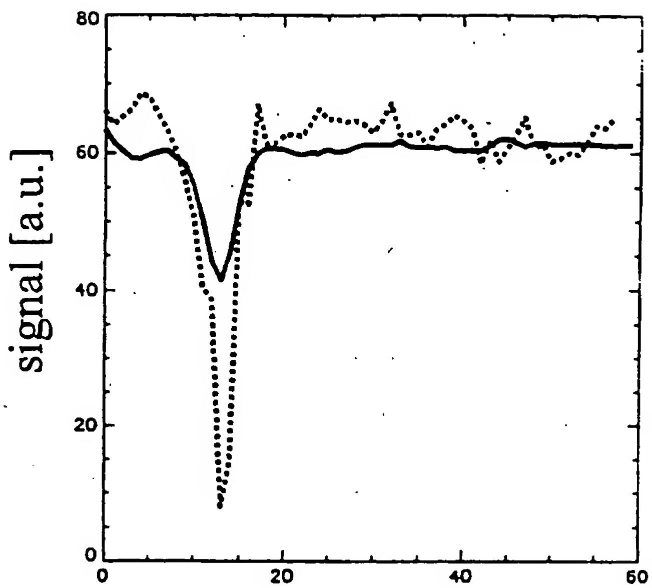
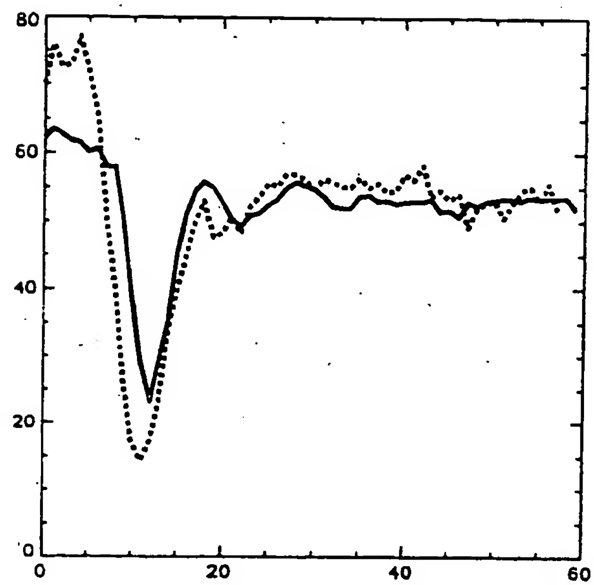


Fig 3b



PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
FRANK B. DEHN & CO.
Attn. COCKBAIN, J.
179 Queen Victoria Street
London EC4V 4EL
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

FILE 70086/002
21 AUG 2000

	Date of mailing (day/month/year) 17/08/2000
Applicant's or agent's file reference 44.70086/002	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB 00/01960	International filing date (day/month/year) 22/05/2000
Applicant NYCOMED IMAGING AS	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2, NL-2280 HV Rijswijk, Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gregory Adam

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, J.
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

FILE 13 JUN 2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.06.2001

Applicant's or agent's file reference	
44.70086/002	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01960	22/05/2000	21/05/1999

Applicant
NYCOMED IMAGING AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Marra, E Tel.+49 89 2399-7235

Form PCT/IPEA/416 (July 1992)

PA NT COOPERATION TREAT

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

COCKBAIN, Julian
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

Date of mailing (day/month/year) 06 November 2001 (06.11.01)	
Applicant's or agent's file reference 44.70086/002	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/01960	**International filing date** (day/month/year) 22 May 2000 (22.05.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
COCKBAIN, Julian Flat 4 83 Linden Gardens London W2 4EU United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Deletion of applicant for GB only due to assignment of rights.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Anman QIU Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 January 2001 (26.01.01)	
International application No. PCT/GB00/01960	**Applicant's or agent's file reference** 44.70086/002
International filing date (day/month/year) 22 May 2000 (22.05.00)	**Priority date** (day/month/year) 21 May 1999 (21.05.99)
Applicant BJØRNERUD, Atle et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

19 December 2000 (19.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was
[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafla Telephone No.: (41-22) 338.83.38

14

PATENT COOPERATION TREATY

REC'D 13 JUN 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 44.70086/002	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01960	International filing date *(day/month/year)* 22/05/2000	Priority date *(day/month/year)* 21/05/1999
International Patent Classification (IPC) or national classification and IPC G01R33/563		
Applicant NYCOMED IMAGING AS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/12/2000	11.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hooper, M Telephone No. +49 89 2399 7438

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-20 as originally filed

Claims, No.:

1-13 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-12.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-12.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 13

	No:	Claims	
Inventive step (IS)	Yes:	Claims	13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	13
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item III

The search examiner found that no search was to be carried out for the subject-matter of claims 1-12, as they fall under the exclusions provided for in Rule 39.1(iv) PCT. The examining authority agrees with the search examiner in this respect, as the independent claims 1 and 2 relate to diagnostic methods, for which no search-report needs to be established (Rule 39.1(iv) PCT) and no preliminary examination needs to be carried out (Rule 67.1(iv) PCT). Furthermore, it is pointed out to the applicant that the methods, in the way they are formulated, can also be regarded as surgical. The step of administering a contrast agent into the vasculature includes the invasive step of injecting the contrast agent, which therefore renders the method surgical in nature.

Re Item V

1. Reference is made to the following document.
   D1: WO-A-92/11037

2. The subject-matter of claim 13 appears, In view of the prior art available from the search report as established, to be novel and inventive, Articles 33(2) and (3) PCT. Document D1 does not show the use of a blood pool agent in the manufacture of a contrast medium for use in a method of diagnosis comprising a method according to any of claims 1-12. This use is also not an obvious modification of the uses described in D1.

   The subject-matter of claim 13 is therefore considered to be novel and inventive, when compared to the prior art available from the search report.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 44.70086/002	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/01960	International filing date *(day/month/year)* 22/05/2000	(Earliest) Priority Date *(day/month/year)* 21/05/1999
Applicant NYCOMED IMAGING AS		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

      [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

      [ ] contained in the international application in written form.
      [ ] filed together with the international application in computer readable form.
      [ ] furnished subsequently to this Authority in written form.
      [ ] furnished subsequently to this Authority in computer readble form.
      [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).
3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 3A, 3B
   [X] as suggested by the applicant.
   [ ] because the applicant failed to suggest a figure.
   [ ] because this figure better characterizes the invention.
   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
GB 00/01960

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, INSPEC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 11037 A (ADVANCED MAGNETICS) 9 July 1992 (1992-07-09) cited in the application page 4, line 18 - line 34 page 6, line 29 -page 7, line 27 page 12, line 27 -page 13, line 28	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2000	17.08.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Volmer, W

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/01960

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1 - 12
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1 - 12

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

Claim 1 specifies:
a method of magnetic resonance imaging of the kidney in a vascularised human body ... permitting both visualisation and gradation of renal artery stenosis and of renal perfusion.

Claim 2 specifies:
a method of differentiation between renovascular damage and renoparenchymal damage in a kidney in a vasularised human body...

Hence, the independent claims 1 and 2 specify:
- a diagnostic method practised on a human body enabling to carry out a diagnostic with respect to the presence ‘visualisation! of renal artery stenosis or its severity ‘gradation!.
or:
- a method of dfferentiation ‘diagnosis! between renovascular damage and renoparenchymal damage.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01960

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9211037 A	09-07-1992	AT 151991 T	15-05-1997
		CA 2097589 A,C	20-06-1992
		DE 69125848 D	28-05-1997
		DE 69125848 T	31-07-1997
		DE 563249 T	03-03-1994
		DK 563249 T	03-11-1997
		EP 0563249 A	06-10-1993
		ES 2059299 T	16-11-1994
		GR 94300001 T	28-02-1994
		GR 3023358 T	29-08-1997
		JP 6503347 T	14-04-1994
		US 5490991 A	13-02-1996
		US 5554386 A	10-09-1996
		US 5589591 A	31-12-1996
		US 5478576 A	26-12-1995
		US 5336506 A	09-08-1994